

BY FACSIMILE: (571) 273-8300

Montreal, Canada

File No.: 6013-114US PP/jp

December 14, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICERECEIVED  
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Patent No.: 6,949,679

DEC 14 2005

Filing date: February 9, 2000

Title of Invention: POLYAMINE TRANSPORT INHIBITORS

Agent of Record: Patrice Préville Tel.: (514) 847-4928

**Certificate of Correction Branch**

Commissioner for Patents

PO Box 1450

Alexandria, VA 22313-1450

USA

Petition under 37 CFR §1.323

Sir,

The Commissioner is hereby petitioned under 37 CFR §1.323 to correct a typographical error in the third named inventor:

“René Charest-Gaudrealt” should read -- René Charest-Gaudreault --.

The typographical error was made in good faith by the applicant in the Declaration at the time of filing the application, and was noted only at the time of publication of the patent.

On December 13, 2005, the agent of record has confirmed with Ms Eva James of the USPTO Certificate of Correction Branch that a petition under 37 CFR §1.323 would be reconsidered.

The petition fee of 100.00\$ in accordance with 37 CFR §1.20(a) should be charged to deposit account number 19-5113.

Enclosed are copies of a correspondence from the USPTO Certificate of Correction Branch dated October 31, 2005 and the cover page of US 6,949,679 for which a certificate of correction is required.

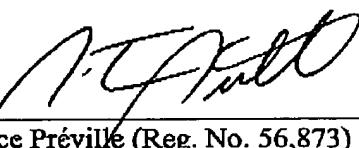
Respectfully submitted,

Patent No. 6,949,679

- 2 -

Richard POULIN et al.

By:



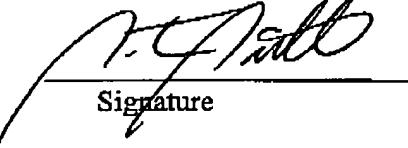
Patrice Prévile (Reg. No. 56,873)  
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Montreal, Quebec, Canada H3A 2Y3  
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Encl.: - Copy of a correspondence from the USPTO Certificate of Correction Branch.  
- Copy of cover page of patent No. 6,949,679.

**CERTIFICATE OF FACSIMILE TRANSMISSION**

I hereby certify that this paper is being facsimile transmitted to the  
Patent and Trademark Office on the date shown below.

Patrice Prévile, Reg. No. 56,873  
Name of person signing certification



Signature

December 14, 2005

Date



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY OF COMMERCE AND  
COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

Date: *10/31/05*

Patent No.: 6,949,679  
Inventor: Richard Poulin, et. al.  
Issued: September 27, 2005  
For: POLYAMINE TRANSPORT INHIBITORS  
Docket No: 6013-114UE5pp/jp

NOV 1 2005

*Reply - Correction*

**DUE ON DEC 31 2005**

Re: Request for Certificate of Correction

Consideration has been given your request for the issuance of a certificate of correction for the above-identified patent under the provisions of Rules 1.322 and 1.323.

Respecting the alleged error of the inventor's names and addresses, the inventor's names and addresses are printed in accordance with the Declaration submitted at the time of filing the application. Therefore, no correction is in order here under Rules 1.322 or 1.323.

In view of the foregoing, your request is hereby denied.

A petition under C.F.R. 1.82 is required to correct the alleged error in an inventor's names and addresses, since the inventor's names and addresses is printed in accordance with the Declaration. Since the was the result of applicant's failure to comply with requirements that the complete and correct names and addresses be indicated, no correction is in order here under the provisions of Rule 1.322 or 1.323, unless a petition is granted.

Any petition under 37 CFR 1.182 should be directed to the attention of the Assistant Commissioner for Patents, using the following mailing address or Fax number.

**BEST AVAILABLE COPY**

Further correspondence concerning this matter should be filed and directed to Decisions and Certificates of Correction Branch. Any response must be filed within a two-month period.

Eva James  
For Cecelia Newman  
Decisions & Certificates  
of Correction Branch  
(703) 308-9390 Ext. 124 or Ext. 102

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ej



US006949679B1

(12) **United States Patent**  
**Poulin et al.**

(10) Patent No.: **US 6,949,679 B1**  
(45) Date of Patent: **Sep. 27, 2005**

(54) **POLYAMINE TRANSPORT INHIBITORS**

(75) Inventors: **Richard Poulin, Sainre-Foy (CA);  
 Marie Audette, Cap-Rouge (CA); Rene  
 Charest-Gaudreault, St. Nicolas (CA)**

(73) Assignee: **Universite Laval, Quebec (CA)**

(\*) Notice: Subject to any disclaimer, the term of this  
 patent is extended or adjusted under 35  
 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/529,319**

(22) PCT Filed: **Apr. 21, 1998**

(86) PCT No.: **PCT/US98/07806**

§ 371 (c)(1),  
 (2), (4) Date: **Feb. 9, 2001**

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PCT Pub. Date: **Oct. 28, 1999**

(51) Int. Cl.<sup>7</sup> **C07C 211/13; C07C 211/22**

(52) U.S. Cl. **564/512**

(58) Field of Search **564/512, 154;  
 514/625; 424/78.27, 78.37, 78.35**

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

3,200,106 A • 8/1965	Dickson et al.	530/231
3,201,472 A • 8/1965	Spivack	564/512
4,631,337 A • 12/1986	Toimala et al.	528/391
4,990,672 A 2/1991	Johnson et al.	
5,456,908 A 10/1995	Aziz et al.	424/78.08
6,083,496 A 7/2000	Poulin et al.	424/78.27
6,673,192 B1 • 1/2004	Woods et al.	156/314

**FOREIGN PATENT DOCUMENTS**

WO	WO93/04373	3/1993
WO	WO 93/12777	7/1993
WO	WO 98/17623	4/1998

**OTHER PUBLICATIONS**

Hubert et al., *Journal of Biological Chemistry*, vol. 271, No. 44, pp 27556-27563, 1996.\*

Patricia Hubesch-Weber et al., *Synthesis and Characterization of a New Series of [12]aneN<sub>x</sub> Type Macrocycles. Structures of two Protonated Metal-Free Ligands*. *Tetrahedron Letters*, Vo. 38, No. 11, pp. 1911-1914, 1997.

Maria Huber et al., *2,2'-Dithiobis (N-ethyl-spermine-5-carboxamide) Is a High Affinity, Membrane-impermeant Antagonist of the Mammalian Polyamine Transport System*. *The Journal of Biological Chemistry*, vol. 271, No. 44, 1996, pp. 27556-27563.

Egon Buhleier et al., *"Cascade"—and "Nonskid—Chain-like" Synthesis of Molecular Cavity Topologies*. Georg Thieme Publishers, pp. 155-158, 1978.

Ask et al., *"Antileukemic effects of non-metabolizable derivatives of spermidine and spermine"*. *Cancer Lett.*, 66:33-38, 1993.

Ask et al., *"Increased survival of L1210 leukemic mice by prevention of the utilization of extracellular polyamines. Studies using a polyamine-uptake mutant, antibiotics and a polyamine-deficient diet"*. *Cancer Lett.*, 66:29-34, 1992.

Aziz et al., *"A novel polymeric spermine conjugate inhibits polyamine transport in pulmonary artery smooth muscle cells"*. *J. Pharmacol. Exper. Ther.*, 274:181-186, 1992.

Aziz et al., *"The potential of a novel polyamine transport inhibitor in cancer chemotherapy"*. *Pharmacol. Exper. Ther.*, 278:185-192, 1996.

Bergeron et al., *"Development of a hyposine reagent for peptide synthesis"*. *Org. Chem.*, 62:3285-3290, 1997.

Chancy et al., *"Tumor selective enhancement of radioactivity uptake in mice treated with  $\beta$ -difluoromethylornithine prior to administration of  $^{11}C$ -putrescine"*. *Life Sci.*, 32:1237-1241, 1983.

Chang et al., *"Modulation of polyamine biosynthesis and transport by oncogene transfection"*. *Biochem. Biophys. Res. Comm.*, 157:264-270, 1988.

Cohen et al., *"Targeting of cytotoxic agents by polyamine synthesis of a chlorambucil-spermidine conjugate"*. *J. Chem. Soc. Chem. Commun.*, pp. 298-300, 1992.

Duranton et al., *"Suppression of preneoplastic changes in the intestine of rats fed low levels of polyamines"*. *Cancer Res.*, 57:573-575, 1997.

Felschow et al., *"Photoaffinity labeling of a cell surface polyamine binding protein"*. *270:28705-28711*, 1995.

Frobort and Adachi, *"Copper/quinone-containing amine oxidases, an exciting class of ubiquitous enzymes"*. *J. Fermentation Bioeng.*, 80:625-632, 1995.

Hayashi et al., *"Ornithine decarboxylase antizyme—A novel type of regulatory protein"*. *Trends Biochem. Sci.*, 21:27-30, 1996.

He et al., *"Antizyme delays the restoration by spermine of growth of polyamine-deficient cells through its negative regulation of polyamine transport"*. *Biochem. Biophys. Res. Commun.*, 203:608-614, 1994.

(Continued)

Primary Examiner—Shailendra Kumar  
 (74) Attorney, Agent, or Firm—Ogilvy Renault

(57) **ABSTRACT**

The present invention describes the design, synthesis and therapeutic use of a variety of novel inhibitors of polyamine transport. The main feature of this class of transport inhibitors is to incorporate a linker or side chain that prevents the uptake of polyamines and helps to conjugate polyamine analogs to form dimers with high inhibitory potency against polyamine uptake. These new compounds incorporate features that are designed to maximize their chemical and metabolic stability and their ability to bind to the polyamine transporter, and to minimize their toxicity by preventing their absorption by the cells. The purpose of such inhibitors is to prevent the uptake or salvaging of circulating polyamines by rapidly proliferating cells such as tumor cells, in order to potentiate the effect of therapeutic inhibitors of polyamine biosynthesis such as alpha-difluoromethylornithine.

4 Claims, 35 Drawing Sheets